

Remarks

The Applicants respectfully requests that the application be reconsidered in view of the above amendment and following remarks.

The present invention relates to the use of compounds, such as cyclic adenosine diphosphate ribose analogues, which are capable of antagonizing a sustained cyclic ADP-ribose (cADPR)-mediated rise in intracellular Ca^{2+} levels in a T cell for modulating T cell activity. The application discloses the applicability of such compounds and demonstrates that there is a cADPR pathway and that this pathway plays a pivotal role in T cell activation. Accordingly, it is demonstrated that the potent Ca^{2+} signaling mediated by the T cell receptor/CD3 complex, and that the molecular target for cADPR in T cells is the type 3 ryanodine receptor/ Ca^{2+} channel. The present invention also provides compounds, which can modulate the activation of T cells via the cADPR pathway in the treatment of autoimmune disease, graft rejections and other T cell dependent abnormalities.

Applicants acknowledge that the Examiner has withdrawn claims 15, 29, 30, and 31.

The Examiner has objected to the drawings because the y-axis of Figure 2 a-e is labeled in Greek. Corrected drawings for Fig. 2 a-f are submitted herewith, thus obviating the Examiners objection to the drawings.

The Examiner has objected to Example 3 because of a typographical error in the citation of a chemical compound. The Examiner specifically objected to Example 3, page 10, however, Example 3 is located on page 29. The Applicants have amended page 29 of the specification, thus obviating the Examiner's objection to example 3.

The Examiner has objected to claim 8 for it depends from cancelled claim 10. By the above amendment, claim 8 is amended to be dependent from claim 1. Claim 8 is

also amended to provide proper antecedent basis to the term patient. No new matter has been added and reconsideration is requested.

Claims 1-5, 8 and 20-28 stand rejected under 35 U.S.C. § 112, first paragraph. The Applicants respectfully submit that the Examiner has taken the position that the specification is enabling for decreasing T cell activation and for treating rheumatoid arthritis using 7-deaza-8-Br-cADPR, however the Examiner has incorrectly rejected the scope of the claims.

With respect to claim 1, Applicants urge that the specification does enable a person of ordinary skill in the art to use the invention commensurate in scope with claim 1. The Examiner has relied heavily on the *In Re Wands* factors in concluding that the specification lacks enablement due to undue experimentation. In *Wands*, the Court holding was inapposite stating "that the specification was enabling with respect to the claims at issue and found the 'there was considerable direction and guidance' in the specification . . ." See MPEP 2164.01(a). It is respectfully submitted that the instant specification also provides considerable direction and guidance in light of the fact that at least one working example has been admittedly demonstrated.

With respect to *Wands* factors 1 (quantity of experimentation) and 2 (amount of guidance presented), the Examiner has taken the position that there has not been provided adequate guidance in the written description for accomplishing such, as only one compound was assessed, out of the numerous compounds that antagonize a sustained cADPR-mediated rise in intracellular Ca²⁺ levels known in the art, let alone the infinite number of compounds that have yet to be screened. The Applicants respectfully disagree with the Examiner for the following reasons.

First, with respect to (1) quantity of experimentation and (2) guidance in the specification, "the test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible . . . if the specification in question provides a

reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” See MPEP 2164.06 quoting *Wands*. Here, the specification specifically teaches:

- Assays for identifying compounds capable of inhibiting cADPR-mediated sustained Ca^{2+} signaling in T cells. See Page 12.
- How a substance affects the CADPR pathway, and that it may do so in several ways. Page 12.
- A preferred class of compounds (Page 7), and “suitable candidate substances” (Page 13, line 5).
- Assays for testing the physiological affects of substances capable of modulating a cADPR pathway. (Page 15).

In sum, the specification (1) teaches preferred and suitable candidate compounds; (2) teaches assays to determine if a compound is useful; (3) teaches assays to verify the effects of the compounds; and (4) includes and admitted working example. Accordingly one of ordinary skill in the art could use the invention commensurate in scope with claim 1. There is a great amount of direction provided by the inventors, and it is respectfully submitted that in light of the guidance provided in the specification, such experimentation would not be undue based upon factors (1) and (2).

Furthermore, with respect to factors (4)(5) and (6) the Examiner has taken the position that there is a great deal of unpredictability in the art, and there is no discernable pattern as to which compound will be effective in which cell type. The Applicants respectfully submit that prior to making Applicants' invention, the only thing demonstrated by the art was that different cellular systems (E.g. T cells vs. sea urchin eggs) respond in a different ways. The area of science was unclear because the cADPR pathway was not known. The present specification discloses the applicability of compounds and demonstrates that there is a cADPR pathway and that this pathway plays a pivotal role in T cell activation. This makes the instant disclosure dealing with thera-

peutic strategies much more meaningful. Accordingly, claim 1 is enabled because in light of Applicants' disclosure, the art is more predictable.

With respect to (3) working example, and (7) breadth of claims, the Applicants believe that the rejection is inappropriate in light of the Examiner's admission that one working example has been demonstrated. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement . . . is satisfied. *In re Fisher*, 427 F.2d. 833, 839 (CCPA 1970). See also MPEP 2164.01(b).

Here, it is admitted that a working example has been shown. Furthermore, the claimed invention bears a reasonable correlation to the entire scope of the claim. Claim 1 does not claim any compound in general, rather it requires compound capable of antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell. Moreover, the specification teaches how to identify such compounds. See page 12, As- says for identifying compounds capable of inhibiting cADPR-mediated sustained Ca^{2+} signaling in T cells. It is respectfully submitted that the claimed invention bears a reasonable correlation to the entire scope of the claim. Accordingly, the invention is enabled and reconsideration is requested.

Independent claim 23 provides:

23.A method of treating a human or animal patient suffering from an immune disorder which method comprises administering to the patient an effective amount of compound capable of antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell, such that T cell activity is modulated.

Applicants submit that claim 23 is also enabled by the specification for the following reasons.

First, the Examiner has admitted that the specification is enabled for decreasing T cell activation and for treating rheumatoid arthritis using 7-deaza-8-Br-cADPR. In light of the Examiners admission that one working example has been demonstrated reconsideration is requested. Furthermore, the use of 7-deaza-8-Br-CaDPR in antigen-induced arthritis as a MODEL system together with the in vitro data clearly suggest that autoimmune diseases with involvement of T cells can be treated successfully with cADPR antagonists. Moreover, as noted above, the specification (1) teaches preferred and suitable candidate compounds; (2) teaches assays to determine if a compound is useful; (3) teaches assays to verify the effects of the compounds; and (4) includes and admitted working example. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement . . . is satisfied. *In re Fisher*, 427 F.2d. 833, 839 (CCPA 1970). See also MPEP 2164.01(b). Reconsideration that claim 23 is enabled by the specification is urged.

Claims 1-5, 8 and 19-28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants respectfully disagree for the following reasons:

First, with respect to the term "modulating" and "modulated" applicants urge reconsideration in light of the fact that modulating is used according to its plain and ordinary meaning and is clear to one of ordinary skill in the art. The detailed specification has also used the term according to its plain and ordinary meaning throughout. For example, on Page 4, the specification makes clear starting on line 17 that the "present invention provides a compound for use in modulating T cell activity which compound is capable of antagonising a sustained cADPR-mediated rise in intracellular Ca²⁺ levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell. The specification continues on line 27 to state that "such substances may be used to modulate T cell activity, for example suppress inappropriate T cell activity in autoimmune reactions or in response to tissue transplantation as an alternative to existing general immunosuppressants such as Cyclosporin A and FK506." The term is used

according to its plain and ordinary meaning throughout the specification, and Applicants urge that it is clear. Reconsideration is requested.

With respect to the term sustained, the Examiner has opined that the term is a relative word that appears indefinite. Applicants have utilized the plain and ordinary meaning of the word sustained meaning to keep up or prolong. Moreover, the specification clearly shows one of ordinary skill in the art the term is being used according to its plain and ordinary meaning. For example, Applicants direct the Examiner attention to Example 1 on page 25. There, sustained is used in the caption. Moreover, the example further demonstrates the plain and ordinary meaning starting on line 26, where it states "The agonistic anti-CD3 antibody OKT3 induced a slowly rising, but sustained increase in intracellular cADPR reaching its highest level 30 min after stimulation, a level that was still maintained after 60 min (Figure 1a). One of ordinary skill in the art would clearly understand the meaning of sustained in light of the specification, examples, and figures. Reconsideration is requested.

With respect to the term "cADPR analogue" in claims 3 and 25 Applicants urge that the term is clear, and requests reconsideration in light of the fact that term cADPR analogue has its plain and ordinary meaning. One of ordinary skill in the art clearly understands that an analogue of cADPR is a chemical compound that is structurally similar to cADPR itself but differs slightly in composition (as in the replacement of at least one atom by at least one atom of a different element or in the presence of a particular functional group). For example, the specification makes this clear to one of ordinary skill in the art that the plain and ordinary meaning of the term is used. See for example, page 7 that states that a particularly preferred class of compounds for use in the present invention are cADPR analogues, for example a compound comprising an adenine component to which is individually linked two ribose moieties or a derivative(s) thereof, which ribose moieties are joined via a pyrophosphate bridging group or a more hydrophobic isostere. Moreover, the specification at the bottom of page 7 shows particular compounds including those of formula 1. In light of the entire detailed specifica-

tion confirming the plain and ordinary meaning of the term "cADPR analogue", Applicants urge that the meaning of the term is clear and reconsideration is requested.

The Examiner has objected to the compound of formula 2, because it is unclear what the counter ion would be to balance the charge of the compound. Applicants urge that since no counterion is claimed, the objection is inappropriate. Reconsideration is urged.

The Examiner has objected to the term "bio-isoster" in claims 5, 20, 27 as indefinite. Applicants submit that the term is specifically defined in the specification and is clear to one of ordinary skill in the art. On page 10, the specification defines bio-isostere as used in the normal sense - namely a similar (but not the same) or a different chemical structure and having the same biological functional effect. Reconsideration is urged in light of the definition provided.

The Examiner has objected to the term Z. Support for Z group being a salt is demonstrated on page 8, where it states that Z is . . . a pharmaceutically acceptable salt. The Z group is further described starting at the bottom of page 9. The applicant respectfully submits that the Z group is clearly defined in the specification, and one of ordinary skill in the art understands what constitutes a pharmaceutically acceptable salt. Z is clear and reconsideration is requested.

The Examiner has objected to the R groups in formulas (3) and (4) as unclear. The specification makes clear on page 11 that A) R_1 and R_2 are independently selected from the group consisting of H, C_1 to C_{20} hydrocarbyl, sugar moieties and phosphate groups; and; B) R_3 is selected from the group consisting of H and C_1 to C_{20} hydrocarbyl, a bio-isostere and a pharmaceutically acceptable salt thereof. The added limitations make clear where the R_1 , R_2 , and R_3 are selected from. The specification also makes clear on page 8, line 16, that R , R^1 , R^2 , R^3 , R^4 and R^6 is independently selected from H and C_1 to C_{10} hydrocarbyl, more preferably H and C_1 to C_5 hydrocarbyl. Reconsideration is requested.

Claim 22 has been amended to provide proper antecedent basis. Reconsideration is requested.

Claims 1-5, 8, and 19-28 have been rejected under 35 U.S.C. 103 (a) as being unpatentable over Sethi *et al.*, *Journal of Biological Chemistry*, in view of Guse (U) and Guse (AC) of record. These rejections are respectfully traversed, and Applicant respectfully requests that the Examiner reconsider the rejection.

Sethi reports on the biological properties of hydrolysis-resistant cADPR receptor antagonist, 7-deaza-8-bromo-cADPR. The Examiner has correctly stated that Sethi does not state that the results of antagonizing the cADPR receptor in T cells would lead to a decrease in T cell activation. Further, the Examiner has correctly stated that Sethi does not specifically state that such antagonist could be used to treat an immune disease. Moreover, Sethi does not teach that the modulation of T cell activation can be accomplished *ex vivo*.

Guse U relates to Ca^{2+} release from intracellular stores. Guse U suggests that evidence is accumulating that CADPr is present endogenously in Jurkat and HPB.ALL T cells and that cADPr dose-dependently and specifically released Ca^{2+} from an intracellular Ca^{2+} pool.

Guse AC is a review article published by one of the inventors of the present application and teaches that Ca^{2+} signaling in response to antigenic stimulation is essential for proliferation of T-lymphocytes and is accordingly one of the important early events in T-lymphocyte signal transduction. The cited document suggests that one aspect of the immunosuppressive effect of FK506 (immunosuppressant) may be to inhibit the cADPR-mediated Ca^{2+} -release. The author has also suggested that targeting T-lymphocyte Ca^{2+} entry channels would have important implications for the development of immunosuppressive drugs.

The Examiner has taken the position that claims 1 is obvious to one of ordinary skill in the art to use cADPR receptor antagonist of Sethi to decrease T cell activation, as Guse U and Guse AC teaches that modulation of cADPR would have implications on T cell activation. The Examiner has further opined that a skilled artisan would have been motivated and have had a reasonable expectation of success, as Sethi teaches that such antagonists would be useful in T cells. Further the Examiner states that it would have been obvious to use such compounds for treatment of an immune disorder as Guse AC teaches that a known immunosuppressant potentially is effective via the method of inactivation.

The applicant respectfully disagrees with the Examiner for the following reasons:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143.

The present invention relates to the use of compounds, such as cyclic adenosine diphosphate ribose analogues, which are capable of antagonizing a sustained cyclic ADP-ribose (cADPR)-mediated rise in intracellular Ca^{2+} levels in a T cell for modulating T cell activity. The application discloses the applicability of such compounds and demonstrates that there is a cADPR pathway and that this pathway plays a pivotal role in T cell activation. Accordingly, it is demonstrated that the potent Ca^{2+} signaling mediated by the T cell receptor/CD3 complex, and that the molecular target for cADPR in T cells is the type 3 ryanodine receptor/ Ca^{2+} channel. The present invention also provides compounds, which can modulate the activation of T cells via the cADPR pathway in the treatment of autoimmune disease, graft rejections and other T cell dependent abnormalities.

With respect to Claim 1, an independent claim from which claims 2-5, 8, 19, 20 and 22 depend, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Independent claim 1 of the claimed invention requires, among other things, the step of administering to the mammal or a mammalian T cell culture an effective amount of a compound capable of antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell. Applicants' disclosure teaches there is a cADPR pathway and that this pathway plays a pivotal role in T cell activation. Applicants were the first to demonstrate that the potent Ca^{2+} signaling mediated by the T cell receptor/CD3 complex, and that the molecular target for cADPR in T cells is the type 3 ryanodine receptor/ Ca^{2+} channel. Without this pathway, there would have been no knowledge available to one of ordinary skill in the art to modify Sethi to antagonize a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, the rise being in response to the stimulation of T cell receptor/CD3 complex of the T cell.

There is no motivation to combine Sethi and Guise U. Guise U fails to teach that there is a cADPR pathway and that this pathway plays a pivotal role in T cell activation. Accordingly, even though Guise concludes that cGMP may be involved in this signaling cascade, linking TCR/CD3 triggering to the formation of cADPr. Absent the Applicants' disclosed mechanism, there is no motivation within the reference to combine Sethi with Guise U to obtain a compound capable of antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell. Accordingly the claimed invention is not obvious.

Moreover, there would be no motivation to combine Sethi with Guise AC, because the cADPR-dependent channels i.e. the type 3 ryanodine receptor/ Ca^{2+} channels as described in the present Application are not Ca^{2+} entry channels. See description,

sentence bridging pages 3-4 and page 7, lines 8-10). Furthermore, although Guse AC states that one aspect of the immunosuppressive action of FK506 may be an inhibitory effect on cADPR-mediated Ca^{2+} release, there is no published data confirming that the FK506-binding protein (FKBO) was indeed the binding protein for cADPR before the present invention. Moreover, Guise AC does not show experimental data supporting a complete cADPR signaling pathway nor does it suggest a role for this complete pathway as an essential step in the activation of T cells.

Guise AC further states that despite the advances in the field, several different aspects of the regulation of Ca^{2+} signaling in T cells are still controversial and need further and more detailed investigation in the future (See Guise AC, page 440 Section VI), thus, highlighting that the mechanism of Ca^{2+} accumulation, i.e. the regulatory pathway responsible for Ca^{2+} accumulation was not at all well understood before the present application. Therefore, it would have been unreasonable to suggest that targeting the Ca^{2+} channels would have the specific effect on T cell activation as described in the present invention, and resulted in the possibility of the elements of claim 1. Absent a reasonable expectation of success, claim 1 is not obvious.

In sum, none of the cited references contain solid data showing that the whole cADPR-signaling pathway is an essential step of T cell activation. One of ordinary skill in the art would have had to show a causal relationship of T cell receptor stimulation, ADP-ribosyl cyclase activation, cADPR generation, calcium signaling, and proliferation. Absent such a showing, there could be no motivation or suggestion to combine the cited references. Applicants' disclosure teaches there is a cADPR pathway and that this pathway plays a pivotal role in T cell activation. Accordingly, Applicants were able to invent claim 1, i.e. antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell. Nothing in the cited references suggests that the references should be combined to arrive at the claimed invention. In order to be obvious, the teaching or suggestion to make the claimed combination *and* the reasonable expecta-

tion of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP 2143. Accordingly, claim 1 is not obvious. It further submitted that the Examiner has used impermissible hindsight reasoning to find the claimed invention obvious.

With respect to Claim 23, an independent claim from which claims 24, 25, 26, 27 and 28 depend, the prior art references (or references when combined) fail to teach or suggest all the claim limitations. Independent claim 23 of the claimed invention requires, among other things, the step of administering to the patient an effective amount of compound capable of antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell, such that T cell activity is modulated.

Sethi says that while the compounds could be used in T cells, and all of the support work was entirely upon invertebrates. One of ordinary skill in the art would not extrapolate or predict that the compounds could be administered to a patient as claim 23 requires.

Moreover, the experiments in Guse AC from which the conclusions were drawn were conducted on sea urchin eggs. However there is no correlation between T cell activation which is regulated by a signal transduction pathway as described by the instant Application. Therefore, it would be unreasonable to suggest that the results from sea urchin eggs make obvious administering compounds of a claimed invention to a patient as required by claim 23.

Nothing in Guse U demonstrates administering compounds to a patient.

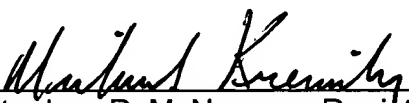
Accordingly, examining and or combining the cited references would not provide a reasonable expectation of success in making the claimed invention. Claim 23 is not obvious. Applicants have demonstrated an admittedly working example and furthered

the art considerable with the discovery of a cADPR pathway which plays a pivotal role in T cell activation. Reconsideration is requested.

There would be no motivation to combine Sethi, Guse AC and Guse U to arrived at the claimed invention of administering the compounds of the invention to a patient and the claim 23 is not obvious.

It is respectfully submitted that new claims 1, 2, 3, 4, 5, 8, 19, 20, 21, 22, 23, 24, 25, 26, 27, and 28, all of the claims remaining in the application, are in order for allowance, and early notice to that effect is respectfully requested. If the Examiner has any questions about this communication he is invited to call Michael Krenicky at (203) 324-6155 to discuss.

Respectfully submitted,



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